D409H/D409H genotype in Gaucher-like disease

We read with great interest the report by Chabas et al. on Spanish sibs with Gaucher disease linked with homozygous D409H (1342C) mutation presenting cardiovascular calcifications. However, they did not cite our article,1 in which we delineated an unusual form of glucocerebrosidase deficiency on the basis of thorough clinicopathological investigations in three Japanese sibs. In fact, the unusual clinical manifestations of their juvenile Spanish patients closely resembled those of our adult Japanese patients, including fatal left sided valvular stenosis with calcification, corneal opacities, and supranuclear opthalmoplegia. Also, communicating hydrocephalus, sensorineural deafness, and deformed toes were present in our Japanese sibs, but common manifestations of Gaucher disease were less evident. This unique syndrome has been classified as "Gaucher-like disease" (McKusick, MIM 231005).1 To determine whether both groups of patients share the same genotype and to establish the tightness of phenotype-genotype correlation in this syndrome, we tested for the D409H mutation of the glucocerebrosidase gene.

Genomic DNA was prepared from a frozen spleen taken at necropsy of patient 1 who died aged 44.1 PCR based screening for the D409H mutation was performed as previously described.2 A segment of the glucocerebrosidase gene spanning exons 9 to 11 was amplified using the oligonucleotide primer pair: 5′-ACCCCGAAGGGAGCCACAT-3′ (sense) and 5′-TGGCTTCTTCGTTGGATACTG-3′ (antisense). To avoid amplifying a pseudogene, PCR was performed for 25 cycles at 94°C for two minutes, at 53°C for three minutes, and at 72°C for three minutes. The resulting 825 bp product was digested with SstI and the digests were resolved on 20% PAGE gel. As shown in fig 1, the proband's genotype was homozygous for the D409H mutation. One of the other mutations including L444P, N370S, P415R, F213L, 844G, IV52+1, and R463C were identified in our screening using previously reported methods.1 Genotyping for the P.1.L and PKLR polymorphism in our case showed the +/− and −/− genotype, respectively.

The prevalence of mutant alleles among Japanese patients with Gaucher disease seems to differ from that observed in affected subjects of Jewish and non-Jewish European ancestry.1 By contrast, the phenotype of the D409H/D409H genotype appears to be identical in such diverse communities as the Spanish,1 Japanese,2 Arab,3 and British.4,5 Thus, there is a particularly tight par-ethnic association between phenotype and genotype in this syndrome. It was remarkable on re-evaluation of our postmortem examination that there was severe connective tissue involvement with a pattern resembling that of other lysosomal storage disorders, particularly the mucopolysaccharidoses (MPS); calcified aortic and mitral stenosis with marked fibrosis resulted from extensive pulmonary involvement, intimal fibrous thickening of the ascending aorta, and leptomeningeal thickening with marked perivascular fibrosis. Furthermore, ultrastructural studies disclosed proliferation of abundant vacuolated Gaucher cells resembling foam cells, in addition to classical Gaucher cells found only in the bone marrow.2,6 These observations, together with the unusually severe "fibrotic changes" in connective tissue, indicate that an additional process is operating. Although we performed repeated urine screening spot tests for MPS,7 assays of eight other kinds of lysosomal enzymes,8 and extensive ultrastructural re-examinations, we could not detect any evidence of other coincidental lysosomal disorders, such as MPS and glycoprotein storage diseases.

As suggested by Mistry,3 the recent discovery of metaxin, a gene contiguous to both thrombospardin 3 and glucocerebrosidase, leads to the possibility of the presence of a contiguous gene syndrome in Gaucher-like disease. However, current investigations indicate no evidence for common metabolic relationships or for structural interactions between corresponding proteins of the metaxin and glucocerebrosidase genes in the human.11 To elucidate the pathogenesis of unusual clinicopathological manifestations in this syndrome, further investigations for the peculiar connective tissue involvement associated with the unique genotype are required.

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